The Association of Blood Urea Nitrogen Levels and Coronary Artery Disease

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ABSTRACT

Renal dysfunction has been associated with adverse cardiovascular outcomes. Estimates of renal function routinely utilize creatinine-based measures. Serum blood urea nitrogen (BUN) levels, however, may provide supplemental information in regard to renal function as renal proximal tubule cells may increase BUN reabsorption in the setting of increased neurohormonal activation. We performed a retrospective chart review on 156 consecutive adult patients presenting to the Montefiore Medical Center Emergency Department with symptoms of unstable angina and no known prior history of coronary artery disease (CAD) who underwent cardiac catheterization as part of their index hospitalization. On multivariate analysis, admission serum BUN was associated with an increased burden of CAD on cardiac catheterization and was not associated with ruling in for myocardial infarction (MI).

INTRODUCTION

Renal dysfunction has been associated with adverse cardiovascular outcomes (McCullough, 2003; Dossetor, 1966; Conte et al., 1987; Aronson et al., 2004). In these studies and others, renal function has routinely been assessed with an estimated creatinine clearance, serum creatinine, or an estimated glomerular filtration rate derived from the serum creatinine (Suwaidi et al., 2002).

Serum blood urea nitrogen (BUN) levels, however, may provide supplemental information in regard to renal function as renal proximal tubule cells may increase BUN reabsorption in the setting of increased neurohormonal activation (Shlipak et al., 2002). Accordingly, higher serum BUN has been associated with adverse outcomes in subjects with acute coronary syndromes (Levey et al., 1999). We examined whether admission serum BUN in subjects presenting with symptoms of unstable angina and without known coronary artery disease (CAD) was associated with the burden of CAD on cardiac catheterization and with ruling in for myocardial infarction (MI).

METHODS

We performed a retrospective chart review on 156 consecutive adult patients presenting to the Montefiore Medical Center Emergency Department beginning on January 1, 2002, with symptoms of unstable angina and no known prior history of CAD who underwent cardiac catheterization as part of their index hospitalization. No known CAD was defined as: no known history of MI, percutaneous coronary intervention, or coronary artery bypass surgery. Additional exclusion criteria were: (1) cardiac catheterization within the previous six months, (2) serum creatinine > 3.0 mg/dl or hemodialysis, (3) a history of heart failure, or (4) other severe acute illness or organ failure. Admission history and laboratory data were obtained. Three patients were missing cardiac enzymes. Creatinine clearance (CrCl) was calculated with the Cockcroft-Gault equation. Hyperlipidemia was defined as a history of hyperlipidemia or anti-hyperlipidemic medication use. Diabetes was defined as a history of diabetes or anti-hyperglycemic medication use. Smoking was defined as any prior history of tobacco smoking. Hypertension (HTN) was defined as a history of HTN or anti-hypertensive medication use. Positive cardiac markers defined ruling in for MI.

A priori, we developed a burden of CAD score, with higher values representing a greater burden of CAD, as described previously (Usberti et al., 1985). We scored the burden of CAD as follows: (1) left main coronary artery; each individual stenosis of 20-49% was given a score of 0.5, 50-69%, 1.0, and >=70%, 1.5, respectively, (2) left anterior descending (LAD) artery system (which included the LAD and diagonals); each individual stenosis of 20-49% was given a score of 0.5, 50-69%, 1.0, and >=70%, 1.5, respectively, (3) left circumflex (LCx) system (which included the LCx and obtuse marginals); each

individual stenosis of 20-49% was given a score of 0.5, 50-69%, 1.0, and >=70%, 1.5, respectively, and (4) right coronary artery (RCA) system (which included the RCA, posterior descending artery and posterior left ventricular branches); each individual stenosis of 20-49% was given a score of 0.5, 50-69%, 1.0, and >=70%, 1.5, respectively. If a ramus branch was present, each individual stenosis of 20-49% was given a score of 0.25, 50-69%, 0.5, and >=70%, 0.75. The score for each individual lesion was totaled into an overall burden of CAD score for each patient. The percent stenoses were obtained from official catheterization reports from one of two experienced interventional cardiologists. The scoring system was considered "appropriate" by three independent cardiologists. The CAD burden score was dichotomized at the 75th percentile.

Table 1: Baseline Patient Characteristics

	Overall* (n=156)
Age	63.2 (+/-) 13.3
Male	52.6%
Creatinine Clearance (mL/min)	94.0 (+/- 59.7)
Diabetes	28.2%
BMI (kg/m^2)	28.3% (+/- 5.9%)
HTN	73.1%
Dyslipidemia	41.6% (2 missing)
Smoking	33.8% (11 missing)
BUN (mg/dl)	17.4 (+/- 6.0)
CAD Burden Score	3.9% (+/- 4.1)

*Three patients are missing cardiac enzymes
BMI = body mass index; BUN = blood urea nitrogen; CAD = coronary artery disease; HTN = hypertension

T-tests and chi square analyses were performed when comparing means and proportions of baseline measurements between subjects with MI and without MI, and between subjects with CAD burdens above and below the 75th percentile, respectively. To evaluate the relationships between serum BUN and CAD burden, and between serum BUN and MI, univariate analyses and multivariate analyses adjusting for baseline characteristics were conducted using logistic regression models. All statistical analysis was performed with the MDAS Version 2.0 (eSKay Software TM 2004) statistical software package. The Montefiore Medical Center Institutional Review Board approved this study.

RESULTS

Baseline characteristics for the entire cohort are presented in Table 1. Baseline characteristics for the dichotomized CAD burden variable are presented in Table 2. The CAD burden score range was 0-19 with a 75th percentile of seven. Subjects with a CAD burden score greater than or equal to the 75th percentile were older (69.2 years vs. 61.0, p=0.04), had lower CrCl (75.7 vs. 100.3, p<0.01), lower BMI (26.5 vs. 28.9, p<0.01), and higher BUN (20.5 vs. 16.5, p<0.01).

On univariate analysis, each 1 mg/dl increase in BUN was associated with an average increased odds of having a CAD burden score greater or equal to the 75th percentile of 12% (OR 1.12 (1.05, 1.19); p<0.01). On multivariate analysis, which included age, sex, CrCl, body mass index, history of smoking, hyperlipidemia, HTN, and diabetes, each 1 mg/dl increase in BUN was associated with an average increased odds of having a CAD burden score greater or equal to the 75th percentile of 9% (OR 1.09 (1.01, 1.12); p=0.02). When MI status during index hospitalization was added to the multivariate model, the association of BUN and burden of CAD remained significant (p=0.05).

Baseline characteristics for those who did and did not rule in for MI are presented in Table 3. Those subjects who ruled in for myocardial infarction had a lower body mass index (BMI) (27.0 mg/dl vs. 29.3 mg/dl, p=0.02), and a higher CAD burden score, (5.2 vs. 2.9, p<0.01), compared with those who did not rule in for myocardial infarction.

On univariate and multivariate analysis, an increased BUN was not associated with an increased odds of ruling in for MI (OR 0.99 (0.07, 1.02); p=0.92) and (OR 0.99 (0.96, 1.05); p=0.82), respectively.

DISCUSSION

We found that elevated serum BUN on admission was associated with an increased burden of CAD on cardiac catheterization during index hospitalization in patients who presented with symptoms of unstable angina and without known cardiovascular disease. To the best of our knowledge, this study is the first to demonstrate this association. Furthermore, each 1mg/dl increase in BUN was associated with an increased burden of CAD. Admission BUN, however, was not associated with ruling in for myocardial infarction.

Blood urea nitrogen may have pro-atherosclerotic effects, as uremia has been associated with an increased burden of oxidative stress (Himmelfarb et al., 2002).

Table 2: Baseline Patient Characteristics by Dichotomized CAD Burden Score

CAD Score	< 75% (n=116)	≥75% (n=40)	p value*
Age	61.0 (+/- 13.5)	69.2 (+/- 10.9)	0.04
Male	50.9%	50.0%	NS
Creatinine clearance (mL/min)	100.3 (+/- 65.4)	75.7 (+/- 33.1)	<0.01
Diabetes	25.7%	35.0%	NS
BMI (kg/m^2)	28.9 (+/- 6.4)	26.5 (+/- 4.1)	<0.01
HTN	71.0%	80.0%	NS
Dyslipidemia	39.4% (2 missing)	47.5%	NS
Smoking	33.0% (7 missing)	36.1% (4 missing)	NS
BUN (mg/dl)	16.5 (+/- 5.2)	20.5 (+/- 7.2)	<0.01

*A p value of <0.05 was considered significant
BMI = body mass index; BUN = blood urea nitrogen; CAD = coronary artery disease;
HTN = hypertension; NS = not significant

BUN may also both inhibit nitric oxide synthesis and promote macrophage proliferation (Moeslinger et al., 1999). Specifically, in vivo studies demonstrate that increasing levels of urea inhibit nitric oxide synthesis in mouse macrophages with concurrent macrophage proliferation (Conte et al., 1987). Furthermore, uremia accelerates atherosclerosis in Apolipoprotein E-deficient mice.

Other studies indicate that uremia induces the expression of osteoblast differentiation factor Cbfa1 in the intima and media of arteries, which may lead to vascular calcification (Moe et al., 2003). Elevated BUN may also serve as a marker of an activated sympathetic nervous system and/or an upregulated renin-angiotensin system, reported promoters of atherosclerosis (Kirtane et al., 2005; Ostfeld et al., 2006; Manuck et al., 1988; Rozanski et al., 1990; Tummala et al., 1999). Activation of these neurohormonal systems has been associated with increased BUN reabsorption in the renal tubules.

We observed this association between increased BUN and CAD while correcting for creatinine clearance. Concurrently, Kirtane et al. (2005) reported that increasing BUN predicts poor outcome in subjects with acute coronary syndromes despite normal or mildly reduced glomerular filtration rates. Consequently, an elevated serum BUN may represent an independent marker of renal dysfunction, which would further support the well-established association between renal disease and CAD (Anvekar et al., 2004; Foley et al., 2005). However, additional study is required to evaluate this point.

Counterintuitively, we found that a reduced BMI was associated with both an increased burden of CAD and with ruling in for myocardial infarction. This finding may be secondary to chance. Alternatively, it may lend support to the "obesity paradox," where overweight or obese patients have greater cardiovascular risk yet appear to have improved outcomes compared to patients who are not overweight or obese (Pingitore et al., 2007).

Our study has several limitations. It is a retrospective analysis. The BUN levels were a single measurement and are not necessarily a reflection of one's chronic level. BUN elevation may occur for reasons other than neurohormonal up-regulation and/or the presence of renal dysfunction, such as bleeding, diuretic or steroid use and/or dietary sources (Mark et al., 1994). No patient in our study, however, had known active bleeding, or was known to be taking loop diuretics or steroids. We were unable to account for potential dietary influences on serum BUN. Furthermore, our measure of the burden of CAD, as previously reported (Usberti et al., 1985), although deemed "appropriate" by three independent cardiologists, has not been validated. However, previous studies have utilized a similar scale in grading coronary artery lesions based on angiographic findings (Warnholtz et al., 1999; Goetz, 1997).

CONCLUSIONS

In conclusion, our study suggests that an elevated serum BUN in subjects presenting with signs and symptoms of unstable angina and without known CAD may predict a larger burden of CAD on cardiac catheterization inde-

Table 3: Baseline Patient Characteristics by Presence or Absence of MI*

	MI (+) (n=68)	MI (-) (n=85)	p value†
Age	63.4 (+/- 12.9)	63.0 (+/- 13.9)	NS
Male	50.0%	55.3%	NS
Creatinine clearance (mL/min)	95.5 (+/- 75.4)	93.9 (+/- 44.7)	NS
Diabetes	20.6%	32.9%	NS
BMI (kg/m^2)	27.0 (+/- 5.1)	29.3 (+/- 6.4)	0.02
HTN	67.6%	76.5%	NS
Dyslipidemia	37.3% (1 missing)	42.9% (1 missing)	NS
Smoking	36.7% (8 missing)	30.5% (3 missing)	NS
BUN (mg/dl)	17.4 (+/- 6.1)	17.5 (+/- 6.0)	NS
CAD burden score	5.2 (+/- 3.9)	2.9 (+/- 4.0)	<0.01

*Three patients are missing cardiac enzymes
†A p value of <0.05 was considered significant
BMI = body mass index; BUN = blood urea nitrogen; CAD = coronary artery disease
HTN = hypertension; MI = myocardial infarction; NS = not significant

pendent of creatinine clearance. Further study is warranted to explore this association.

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